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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/731,759

12/08/2003

David John King

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4275

34133

7590

12/26/2008

COZEN O'CONNOR, P.C.

1900 MARKET STREET

PHILADELPHIA, PA 19103-3508

EXAMINER

SANG, HONG

ART UNIT

PAPER NUMBER

1643

MAIL DATE

DELIVERY MODE

12/26/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/731,759	Applicant(s) KING ET AL.	
	Examiner HONG SANG	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 October 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RE: King et al.

1. The examiner of your application in the PTO has changed. To aid in correlating of any papers for this application, all further correspondence regarding this application should be directed to Examiner Hong Sang, Art Unit: 1643.
2. Applicant's response filed on 10/8/2008 is acknowledged. Claims 11-16 are pending. Claims 1-10 have been cancelled. No claims have been amended.
3. Claims 11-16 are under examination.

Rejections Maintained

Claim Rejections - 35 USC § 103

4. The rejection of claims 11-16 under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (FASEB J. 1995. 9:A1479; IDS-12/13/2004) in view of Griffiths et al (U.S. Patent 5,670,132, Date Filed: 09/20/1994; IDS – 12/13/2004) is maintained.

The response states that there is no motivation to modify Zapata et al. to derive Applicants' invention, and Griffiths et al. does not describe a PEG of 30,000 Da. It provides a range of suitable PEGs having molecular weights of 1,000-30,000 (col. 3, lines 12-15). The disclosure of a range is not a disclosure of the endpoints of the range. Further, Griffiths et al. actually teaches away from Applicants' invention. Applicants' claims recite that the fragment comprises a hinge region with a single cysteine, to which the polymer, e.g., PEG, is attached. Griffiths et al. teaches that the radiolabel is to be

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attached to a hinge region cysteine. Thus, if a single cysteine is present in the hinge region of the fragment, it is to be radiolabeled, not pegylated.

Applicant's arguments have been carefully considered but are not persuasive. Zapata et al teach a Fab' fragment which contains a single free thiol in the hinge region including the coupling of monomethoxypoly(ethylene glycol) (MePEG) to the thiol, wherein the MePEG is 5 kDa or 10 kDa (see abstract). Zapata et al. disclose that both 5 kDa and 10 kDa MePEG-Fab' species have reduced clearance compared to the native Fab' molecule, with that of the 10 kDa form reduced further than the 5 kDa form (see the abstract). Griffiths et al teach site specific conjugation of PEG to Fab or Fab' (see column 2, lines 46-58) outside the variable region (see column 3 and 4), including a thiol group in the hinge region of the antibody (see column 3, line 24). Griffiths et al. teach that PEG preparations with a wide variety of average molecular weight can be prepared and used for this invention (see column 3, lines 12-13), for example PEGs having average molecular weight of the PEG can be 1,000-30,000 Da (column 3, lines 12-19), which overlaps with the claimed range 25,000 Da-40,000 Da. Griffiths et al further teach an antibody conjugated to 1-10 PEG-5,000 moieties to reduce renal uptake and retention of the PEGylated antibody fragment after radiolabeling (claim 15 and 16, in particular), indicating a wide variety of average molecular weight can be used for PEGylation of an antibody. MPEP §2144.05 states that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Furthermore,

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although Griffiths et al. teach that the radioisotope can be linked to the thiol group in the hinge region, it is not the only site for linking the radioisotope. Griffiths et al. teach thiolating the antibody fragment by introduction of ligands containing thiol groups by conventional procedures, either non-site specifically or on a carbohydrate moiety, preferably one which has been engineered onto a light chain constant region of the fragment (see column 5, lines 10-15). As such Griffiths et al. do not teach away from the instant invention. In view of the teachings of Griffiths et al. that a wide variety of average molecular weight can be used for PEGylation of an antibody, including 5,000-30,000 Da, one of ordinary skill in the art would have been motivated to make a 'MePEG-Fab' using a higher molecular weight such as 25,000-30,000 kDa of MePEG. Moreover, Zapata et al. have shown that higher molecular weight of 10 kDa reduced further clearance compared to the 5 kDa MePEG. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

5. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Hong Sang/
Examiner, Art Unit 1643
12/15/2008

/Christopher H Yaen/
Primary Examiner, Art Unit 1643